International Journal of Science Academic Research
Vol. 06, Issue 07, pp.10333-10338, July, 2025
Available online at http://www.scienceijsar.com

ISSN: 2582-6425

Research Article

COMPARATIVE EFFECTS OF AQUEOUS LEAF AND BARK EXTRACT OF *CORDIA DICHOTOMA* (ANONANG) ON TESTICULAR HISTOPATHOLOGY OF MALE WISTAR RATS

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Received 20th May 2025; **Accepted** 25th June 2025; **Published online** 31st July 2025

Abstract

This study aimed to evaluate the comparative effects of aqueous leaf and bark extracts of *Cordia dichotoma* on the testicular histopathology of male Wistar rats. Thirty young adult male rats, aged 8 to 10 weeks and weighing between 200 and 300 grams, were divided into three groups. Group I received a low concentration of the aqueous leaf and bark extract (3 mL), Group II received a moderate concentration (4 mL), and Group III received a high concentration (5 mL). The treatments were administered via intraperitoneal injection for 21 days. Twenty-four hours after the final treatment, all rats were individually weighed and anesthetized with 95% ethanol before their testes were dissected for histopathological examination. The tissue sections of the testes displayed uniform degenerative changes in the seminiferous tubules. Groups I and II, which received the leaf extract, along with all groups that received the bark extract, exhibited a reduced number of spermatozoa in the centers of the tubules. In contrast, Group III, which also received the leaf extract, showed a significantly higher presence of spermatozoa, constituting 70% of the tubule area. Additionally, moderate intertubular edema was observed in Groups I and II, which were administered the leaf extract. All groups exhibited signs of necrosis and degenerative changes in the tubules. Notably, 25% of the tubules at the periphery lacked spermatogenic cells. Both aqueous extracts resulted in testicular changes that could potentially lead to infertility. These effects are attributed to the extracts' inhibitory impact on spermatogenesis and the possible induction of abnormal spermatozoa.

Keywords: *Cordia dichotoma*, Aqueous extract, Histopathology, Testes.

INTRODUCTION

Rat testes are essential for producing spermatozoa, which are crucial for breeding. Researchers around the world have traditionally agreed on using rodent models for biomedical research due to their anatomical, physiological, and genetic similarities to humans. This enhances the accuracy and interpretability of the results (Bryda, 2013). According to the World Health Organization (WHO), between 70% and 90% of people globally, particularly in developing countries, rely on plant-derived medicines to address their health needs (WHO, 2011). There are an estimated 374,000 plant species, of which approximately 28,187 are recognized as medicinal. WHO has documented over 20,000 species of medicinal plants and identified them as potential sources of new drugs (Vaou *et al.,* 2021; Pant *et al.,* 2021). While medicinal plants are generally considered safer and more effective than synthetic drugs, they are not completely free of side effects or toxicity. Research indicates that plant-derived products can produce toxic effects due to secondary metabolites, which may lead to prolonged vascular resistance in rodent embryos and result in teratogenic effects (Ouedraogo *et al.,* 2012). *Cordia dichotoma* G. Forst., commonly known as Anonang, is a small to moderate-sized deciduous tree belonging to the family Boraginaceae. It is widely found in the Philippines (Ragasa *et al.,* 2015). *Cordia dichotoma* has been used in Ayurvedic, Unani, and modern herbal medicine for various ailments since ancient times (Tripathi, 2023). Different parts of the plant have demonstrated a range of properties, including anti-ulcer, contraceptive, anti-inflammatory, antihelmintic, analgesic, anticancer, antioxidant, antimicrobial, antifungal, hepatoprotective, and diuretic effects. These properties make it useful in addressing issues related to the digestive system, respiratory conditions, urogenital health, cardiac problems, vascular concerns, and blood disorders (Prajapati *et al.,* 2017). Despite the reported therapeutic potential of *Cordia dichotoma*, there is a limited number of comprehensive scientific studies that have confirmed or disproven its effects on rat testes. Therefore, this study aims to expand the existing literature on the comparative effects of aqueous leaf and bark extracts of *Cordia dichotoma* on testicular histopathology in male Wistar ratsRat testes are responsible for producing spermatozoa, which are vital for breeding purposes. Researchers worldwide have historically agreed on using rodent models for biomedical research due to their anatomical, physiological, and genetic similarities to humans. This makes the results more accurate and interpretable. Additionally, rodents are small, easily manipulated, adaptable, and affordable for research. Medicinal drugs have been used for contraceptive purposes since ancient times, and these drugs require pharmacological assessment (Malpani, *et al.,* 2020). *Cordia dichotoma* G. Forst.,locally known as Anonang, belonging to the family Boraginaceae,is a small to moderate-sized deciduous tree thatgrows widely in the Philippines (Ragasa, et al.,2015).Different parts of the plant have been documented to demonstrate properties such as anti-ulcer, contraceptive, anti-inflammatory, antihelmintic, analgesic, anticancer, antioxidant, antimicrobial, antifungal, hepatoprotective, and diuretic effects, and they are used for addressing issues related to the digestive system, respiratory conditions, urogenital health, cardiac problems, vascular concerns, and blood disorders (Prajapati *et al.,* 2017). Some

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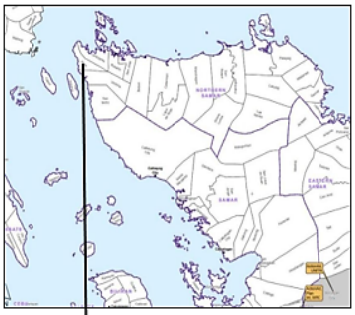
Cordia species, including Cordia sinensis, are conventionally used for birth control by tribal women from the Meena community in Rajasthan, India (Sharma, *et al.,* 2015). Despite these contraceptive potentials reported for *Cordia dichotoma*, there are only a few in-depth scientific studiesinvestigating the exact mechanism of action in male reproduction. Hence, the present study was undertaken to extend the existing literature dealing with the evaluation of the comparative effects of the aqueous leaf and bark extract of *Cordia dichotoma* on testicular histopathology of male Wistar rats.

METHODOLOGY

Locale of the Study

The study was conducted at the University of Eastern Philippines Integrated Research Laboratory (UEP-IRL) from July to September 2023. The University of Eastern Philippines (UEP) is situated on the western boundary of Catarman, Northern Samar, with coordinates of 12° 29' 46" N and 124° 38' 19" E. Leaves and bark samples of *Cordia dichotoma* G. Forst., commonly known as Anonang, were collected in Allen, Northern Samar, Philippines (see Figures 1-2).

Figure 1. Philippine Map



Barangays of Allen Northern Samar	
Map ID	Name
1	Cabacungan
2	Calarayan
3	Guin-arawayan
4	Lipata
5	Tasvilla
6	Santa Rita
7	Victoria
8	Kinaguitman
9	Alejandro Village
10	Lagundi
11	Londres
12	Sabang Zone I
13	Lo-oc
14	Sabang Zone II
15	Kinabranan Zone I
16	Bonifacio
17	Kinabranan Zone II
18	Imelda
19	Jubasan
20	Frederic

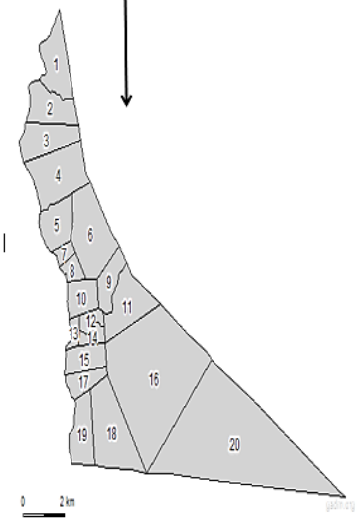


Figure 2. Map of Allen, Northern Samar

The origin and historical distribution of Cordia species remain unclear. Allen, located at 12° 29' 59.99" N and 124° 16' 60.00" E, is a fifth-class municipality in the northwestern part of Northern Samar. It comprises 20 barangays and has a total population of 25,228, according to Phil Atlas in 2022. The majority of its growing population relies on natural resources for their livelihoods, primarily through coconut production, farming, livestock raising, and fishing (PSA, 2015).The study was conducted at the University of Eastern Philippines Integrated Research Laboratory (UEP-IRL) from July to September 2023. The University of Eastern Philippines (UEP) is located at the western boundary of Catarman, Northern Samar (12° 29' 46" N, 124° 38' 19" E).The leaves and bark of *Cordia dichotoma* G. Forst., commonly known as Anonang, were collected in Allen, Northern Samar, Philippines (see Figures 1-2). The origin and historical distribution of the Cordia species remain unclear. Allen, located at 12° 29' 59.99" N, 124° 16' 60.00" E, is a fifth-class municipality in the northwestern part of Northern Samar, Philippines. It comprises 20 barangays and has a total population of 25,228, as reported by Phil Atlas in 2022.The majority of its continuously growing population depends on these natural resources for their livelihood on coconut production, farming, livestock-raising, and fishing (PSA, 2015)

Experimental design and animals

The study utilized an experimental method to investigate the effects of aqueous leaf and bark extracts of *Cordia dichotoma*on testicular histopathology of male Wistar rats. Qualitative analyses were conducted to explore the relationships between the variables. A total of 30 healthy, young adult male Wistar rats, aged between 8 to 10 weeks and weighing between 200-300g, were utilized. The animals were uniquely identified according to their body weights and were housed in screened cages under standard conditions of 22±3°C, with a relative humidity of 30-70%. They were maintained on a 12-hour light/dark cycle and provided with standard pellets and distilled water ad libitum, as per OECD guidelines (2001). The rats underwent a one-week acclimatization period in their cages to ensure normal growth and behavior before the commencement of the experiment. After the acclimatization period, the rats were randomly assigned to three leaf-treated groups (n=5) and three treated-bark groups (n=5).

The initial body weight of the animals was recorded before the start of the treatments and then at least once a week until the treatments were completed. The rats were subjected to a fasting period overnight, during which they had ad libitum access to water. After this fasting period, the rats were weighed, and the test substance, *Cordia dichotoma* extract, was administered intraperitoneally at concentrations of 3 mL, 4 mL, and 5 mL for 21 days.After 24 hours following the last treatment, each rat was weighed individually, anesthetized with 95% ethanol, and then the testeswere dissected for histopathological analysis. All experimental protocols and procedures involving the animals were conducted following the ethical guidelines established by the Institutional Animal Care and Use Committee at the College of Veterinary Medicine, University of Eastern Philippines Main Campus, University Town, Northern Samar.

Procurement of Plants

Fresh leaves and bark of *Cordia dichotoma* G. Forst. were collected from local areas in Allen, Northern Samar, Philippines. They were taken to the University of Eastern Philippines Integrated Research Laboratory (UEP-IRL) to prepare for extraction and their use as treatment variables in the experiment.

Plant Extraction

A sample of 100 grams of fresh leaves and bark from *Cordia dichotoma* was carefully washed under running tap water,

followed by a final rinse with distilled water. The washed leaves and bark were then boiled in 1000 mL of distilled water at a ratio of 1:16 to prepare the extract. After boiling for 15 minutes, the solution was set aside to cool and was subsequently filtered using filter paper. The resulting aqueous extract of the leaves and bark of *Cordia dichotoma* was used to assess its effects on the rat testes.

Test Substances Administration

The animals were randomly assigned to three (3) groups, each consisting of five (5) animals, to conduct histopathological analysis. The treatment groups were designated as follows:

Group I received a low concentration of aqueous leaf and bark extract of *Cordia dichotoma*at a dose of 3 mL.

Group II received a moderate concentrationof aqueous leaf and bark extract of *Cordia dichotoma*at a dose of 4 mL.

Group III received a high concentration ofaqueous leaf and bark extract of *Cordia dichotoma*at a doseof 5 mL.

The experimental groups were given the plant extract via intraperitoneal administration at similar times each day (between 1:00 and 5:00 P.M.). In rare cases where a single concentration was not feasible, it could be divided into smaller fractions to be administered within 24 hours, following OECD Guidelines. After administration of the substance, food was withheld for an additional 3 to 4 hours.

Histopathological Analysis

Rat testes were carefully dissected after an abdominal incision. The samples were subsequently isolated, weighed, and fixed in a 10% formalin solution at a 5:9 ratio for a minimum duration of 48 hours. After fixation, the samples were submitted to Vet Central Lab, Animal Diagnostic Laboratory Services in the Philippines, where they were processed for analysis. A thick section, measuring 5-6 µm, was prepared and stained with hematoxylin and eosin (H&E). The stained sections were then examined under a light microscope at a magnification of 40x to evaluate the testicular histopathological changes of the experimental animals.

RESULTS AND DISCUSSION

Figure 3 shows the effects of the aqueous leaf extract of *Cordia dichotoma* on the histopathological examination of the testis section in male Wistar rats after21 days. Examined sections of all leaf-treated groups revealed a normalstructure characterized by round to elongated ovoid seminiferous tubules. These tubules were lined with several layers of spermatogenic cells and Sertoli cells, with spermatozoa occupying the tubular lumen. However,all treated groups showed that some tubules at the periphery were devoid of spermatogenic cells, exhibiting necrosis and degeneration, which was observed in 25% of the tubules. In the leaf-treated group receiving a concentration of 5mL, about 70% of seminiferous tubules contained a few spermatozoa at their center, compared to only 50% in the3 mL and 4mL leaf-treated groups. Furthermore, the leaf-treated groups that received concentrations of 3mL and 4 mL displayed moderate intertubular edema (see Figure 3 (A-B)).

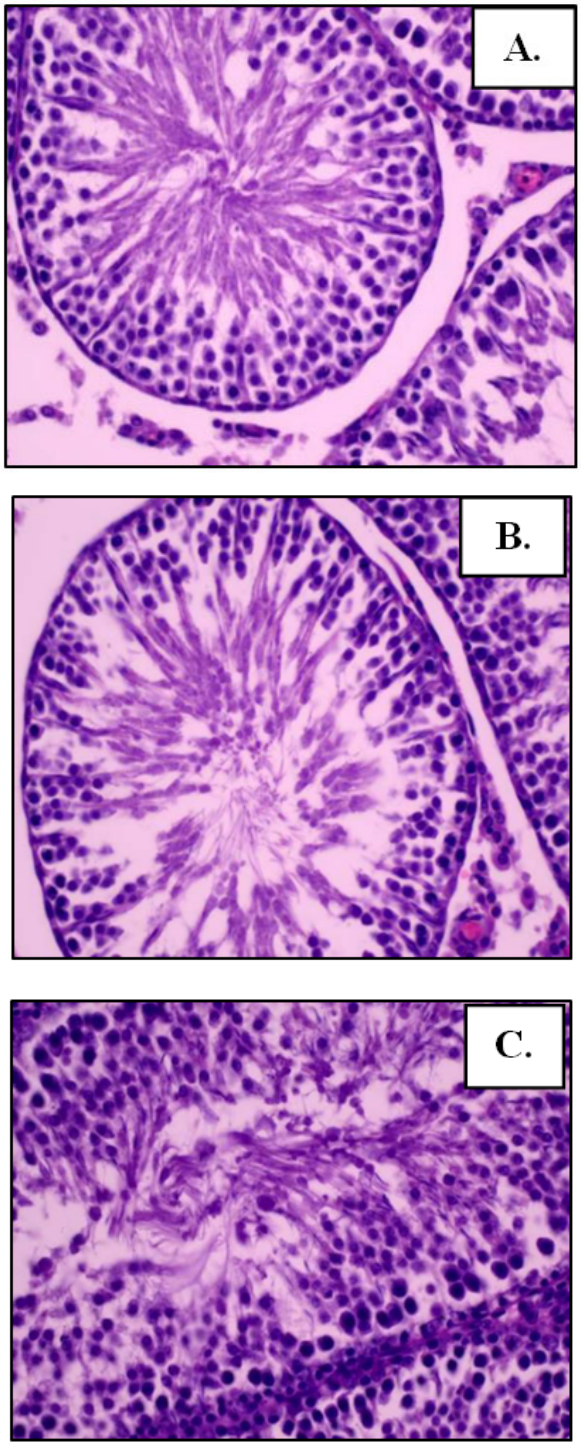


Figure 3. Photomicrograph of a rat's testicular cross-section treated with aqueous leaf extract of *Cordia dichotoma* (40x, H&E stained)

Figure 4 shows the effects of the aqueous bark extract of *Cordia dichotoma* on the histopathological examination of the testis section in male Wistar rats after21 days. Examined testicular sections of the bark-treated groups showed the normal structure of round to elongated ovoid seminiferous tubules, which are lined with multiple layers of spermatogenic and Sertoli cells, while spermatozoa filled the tubular lumen. However, uniform degenerative changes were observed across all treated groups. Some seminiferous tubules contained only a few spermatozoa at their center (50%), while 25% of tubules at the periphery were devoid of spermatogenic cells, showing signs of necrosis and degeneration (see Figure 4 (A-C)).

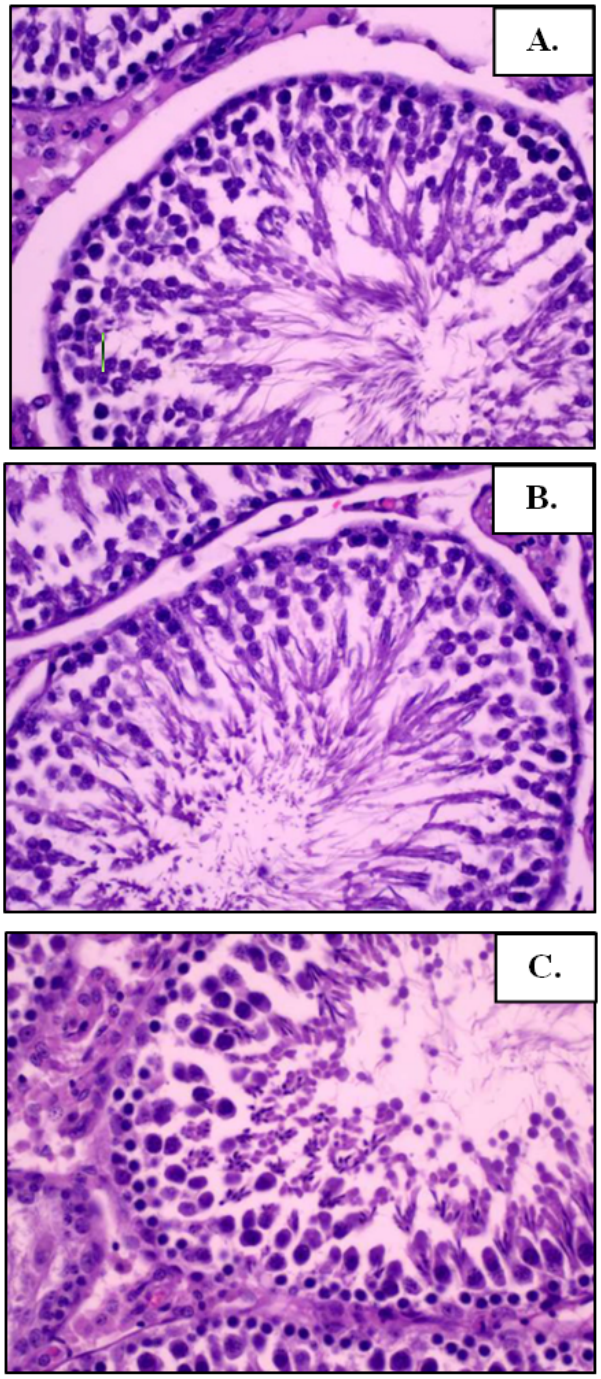


Figure 4. Photomicrograph of a rat's testicular cross-section treated with aqueous bark extract of *Cordia dichotoma*

The observed effects can be attributed to the steroidal glycosides and saponins found in the leaves, which inhibit enzyme activity stimulated by estrogen in various estrogen-sensitive tissues (Bhattacharya and Saha, 2013).This finding is consistent with research by Katolkar *et al.* (2012), which suggested that the different phytoestrogens found in the crude methanolic extract of C. dichotoma bark (BCD) could be responsible for its anti-implantation effects. Excessive consumption of these natural plant compounds (phytoestrogens) may have adverse effects on the reproductive system and reduce fertility (Csupor-Löffler *et al.,* 2009). Additionally, the results support the findings of El-Newary et al. (2022), indicating that in the group treated with 125 mg of Cordia for 28 days, microscopic analysis showed minor atrophy of the seminiferous tubules along with mild interstitial edema. The group receiving 250 mg of Cordia for the same duration exhibited testicular sections with slight atrophy of the seminiferous tubules, mild interstitial edema, and congestion of blood vessels within the testes. Conversely, the sections from the group treated with 500 mg/kg revealed significant atrophy of the seminiferous tubules and mild degenerative changes. This effect may be attributed to the presence of certain estrogenic compounds in the leaves, such as steroidal glycosides and saponins, which have been previously shown to inhibit the function of estrogen-induced enzymes in various tissues targeted by estrogen (Bhattacharya and Saha, 2013).This finding agrees with the study of Katolkar, *et al.,* (2012) showed that thepresence of various phytoestrogens in crude methanolic extract of C. dichotoma Bark (BCD), like saponins, glycosides, and flavonoids, might be responsible for its anti-implantation activity. The seminiferous tubules make up 80% of the total mass of the testis. Distortion in these tubules can occur due to the loss of germ cells from cellular degeneration and the separation of Sertoli cells from the basal lamina. This leads to a reduction in their diameter caused by tubule atrophy and significant spermatogenic necrosis (Parhizkar *et al.,* 2014). Necrosis refers to the death of cells or tissues within living organisms, resulting in an impairment of the ability of these cells to effectively absorb nutrients due to damage. In male rats, spermatozoa are produced through spermatogenesis that takes place in the seminiferous tubules of the testes. The quality of these spermatozoa is crucial for successful fertilization (Susetyarini and Ariesandy, 2016). Moreover, research has shown that the disruption caused by toxic substances during spermatogenesis leads to degenerative changes in both the seminiferous tubules and interstitial cells within the testes of rats (Thakur *et al.,* 2014).Excessive consumption of natural plant compounds (phytoestrogens) can affect the reproductive system and reduce fertility (Csupor-Löffler *et al.,* 2009). These findings further supported the report of El-Newary, *et al.,* (2022)that the group treated with 125mg of Cordia for 28 days, microscopic examination revealed slight atrophy of the seminiferous tubules, accompanied by mild interstitial edema. The group administered 250 mg of Cordia for 28 days exhibited testicular sections showing minor atrophy of seminiferous tubules, mild interstitial edema, and congestion of blood vessels in the testes.

In contrast, the sections examined from the 500mg/kg-treated group displayed severe atrophy of seminiferous tubules along with mild degeneration. Furthermore, seminiferous tubules comprise 80% of the testicular mass, distortion in seminiferous tubules is due to the loss of germ cells by cell degeneration and detachment of Sertoli cells from the basal lamina resulting in the decrease in diameter due to atrophy of the tubules, massive spermatogenic necrosis (Parhizkar, *et al.,* 2014). Necrosis is the death of cells or tissues in living organisms, and as a result, these cells can no longer function in taking nutrients because they have been damaged. Spermatozoa of male rats are produced from the process of spermatogenesis in the seminiferous tubules of the testes. The quality of spermatozoa determines fertilization success (Susetyarini and Ariesandy, 2016). Therefore, the interference of a toxic substance with the spermatogenesis process has been reported to induce degenerative changes in the seminiferous tubule and interstitial cells in the testis of rats (Thakur, *et al.,* 2014).

Conclusion and Recommendation

Findings from this study show that administration of aqueous leaves and bark extract of *Cordia dichotoma*in male Wistar ratsrats caused testicular damage, which is evident in

degenerative and necrotic changes of the seminiferous tubules. These changes may contribute to infertility due to the extract's inhibitory effects on spermatogenesis and the potential induction of abnormal spermatozoa. Further investigation is necessary to elucidate the precise mechanisms of action and to isolate the phytochemical constituents responsible for the possible male contraceptive agent.

Limitation of the study

The decoction method was selected to extract the leaves and bark of *Cordia dichotoma*, as other extraction techniques were either unavailable or insufficient to yield the required volume of samples for the research. Consequently, the dosage of the extracted substance administered to the experimental rats was not determined based on their body weights; rather, it was calculated according to an appropriate volume suitable for rats with similar or nearly equivalent body weights. Furthermore, due to unexpected incidents of cannibalism among certain animal groups before the treatment period, the number of experimental animals required was reduced. The researchers faced significant challenges in replacing the deceased rats because there was a limited supply of animals that met the necessary age and size specifications. Consequently, no comparisons could be made between the control group and the treatment groups. Therefore, the findings obtained necessitate further investigation and validation.

Acknowledgment

We acknowledge the Vet Central Laboratory, Animal Diagnostic Laboratory Services, and Univet Veterinary Clinic staff for their patience, suggestions, and expertise. College of Science, College of Veterinary Medicine, Integrated Research Laboratory, and Chemistry Laboratory for the laboratory, reagents, equipment, and apparatus used in data analysis. Dr. Joey Marvin C. Carpio, Head of the Institutional Animal Care and Use Committee (IACUC) of the College of Veterinary Medicine, University of Eastern Philippines, for his assistance in reviewing and approving the care and use of animals in this study.

Conflict of interest: The researcher(s) declare no conflict of interest.

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